International Journal of Neuropsychopharmacology (2010), **13**, 305–320. Copyright © CINP 2009
doi:10.1017/S1461145709990423

ARTICLE

CINP

Extended-release quetiapine fumarate (quetiapine XR): a once-daily monotherapy effective in generalized anxiety disorder. Data from a randomized, double-blind, placebo- and active-controlled study

Borwin Bandelow[1], Guy Chouinard[2], Julio Bobes[3], Antti Ahokas[4], Ivan Eggens[5], Sherry Liu[6] and Hans Eriksson[6]

[1] *Department of Psychiatry and Psychotherapy, University of Goettingen, Germany*
[2] *Departments of Psychiatry and Medicine, Université de Montréal and McGill University, Montreal, QC, Canada*
[3] *Department of Psychiatry, University of Oviedo, Oviedo, Asturias, Spain*
[4] *Mehilainen Clinic, Helsinki, Finland*
[5] *AstraZeneca R&D Södertälje, Sweden*
[6] *AstraZeneca Pharmaceuticals, Wilmington, DE, USA*

Abstract

The efficacy and tolerability of extended-release quetiapine fumarate (quetiapine XR) once-daily monotherapy in generalized anxiety disorder (GAD) was assessed. This multicentre, double-blind, randomized, placebo- and active-controlled, phase III trial consisted of a 1- to 4-wk enrolment/wash-out period and a 10-wk (8-wk active treatment, 2-wk post-treatment drug-discontinuation) study period; 873 patients were randomized to 50 mg or 150 mg quetiapine XR, 20 mg paroxetine, or placebo. Primary endpoint was change from randomization at week 8 in Hamilton Rating Scale for Anxiety (HAMA) total score. At week 8, all active agents produced significant improvements in HAMA total and psychic subscale scores *vs.* placebo; HAMA somatic subscale scores were significantly reduced only by 150 mg quetiapine XR. Significant separation from placebo (−2.90) in HAMA total score was observed at day 4 for 50 mg quetiapine XR (−4.43, $p<0.001$) and 150 mg quetiapine XR (–3.86, $p<0.05$), but not for paroxetine (–2.69). Remission (HAMA total score $\leqslant 7$) rates at week 8 were significantly higher for 150 mg quetiapine XR (42.6%, $p<0.01$) and paroxetine (38.8%, $p<0.05$) *vs.* placebo (27.2%). The most common adverse events (AEs) were dry mouth, somnolence, fatigue, dizziness, and headache, for quetiapine XR, and nausea, headache, dizziness for paroxetine. A lower proportion of patients reported sexual dysfunction with quetiapine XR [0.9% (50 mg), 1.8% (150 mg)] than with placebo (2.3%) or paroxetine (7.4%). The incidence of AEs potentially related to extrapyramidal symptoms was: quetiapine XR: 50 mg, 6.8%, 150 mg, 5.0%; placebo, 1.8%; and paroxetine, 8.4%. Once-daily quetiapine XR is an effective and generally well-tolerated treatment for patients with GAD, with symptom improvement seen as early as day 4.

Received 15 December 2008; Reviewed 2 March 2009; Revised 25 June 2009; Accepted 10 July 2009; First published online 20 August 2009

Key words: Extended-release quetiapine fumarate, generalized anxiety disorder, randomized, placebo- and active-controlled study, monotherapy, once-daily.

Introduction

Generalized anxiety disorder (GAD) is a prevalent and chronic illness, having high comorbidity with psychiatric disorders, particularly depression, and physical illness (Nutt *et al*. 2006). GAD is also associated with significant functional impairment and reduced quality of life (Ninan, 2001).

Based on clinical studies in the 1970s and 1980s, conventional antipsychotics were prescribed in Europe for patients with anxiety disorders (Mendels *et al*. 1986; Rickels *et al*. 1978; Yamamoto *et al*. 1973), but at lower doses than for the treatment of schizophrenia (Mendels *et al*. 1986). However, in the USA, conventional antipsychotics were not generally

Address for correspondence: Professor Dr B. Bandelow, Department of Psychiatry and Psychotherapy, University of Goettingen, Von-Siebold-Str. 5, D-37075 Goettingen, Germany.
Tel.: +49-551-396607 *Fax*: +49-551-398952
Email: Borwin.Bandelow@medizin.uni-goettingen.de

used, and were never licensed, for the treatment of GAD.

Currently, the preferred long-term treatment options for GAD include selective serotonin reuptake inhibitors (SSRIs; Allgulander *et al*. 2004) and serotonin-norepinephrine reuptake inhibitors (SNRIs; Gelenberg *et al*. 2000), with benzodiazepines (Chouinard, 2004) used in the short term. In Europe, the calcium channel modulator pregabalin is licensed for the treatment of GAD, but this agent was not approved by the US Food and Drug Administration. Additionally, buspirone is licensed for, and often prescribed for, GAD, although the efficacy data are inconsistent (Bandelow *et al*. 2008).

The search for alternative treatment options is warranted since $<40\%$ of patients with GAD achieve recovery despite receiving pharmacotherapy with SSRIs, benzodiazepines or other antidepressants (Rubio & Lopez-Ibor, 2007). Although there is a paucity of randomized, controlled studies examining treatment strategies for patients with symptomatic GAD following first-line therapy, case-report data suggest that combination therapy with antidepressants and benzodiazepines may be effective (Pollack, 2001). SSRIs and SNRIs have a delayed onset of action (2–4 wk) (Allgulander *et al*. 2004; Gelenberg *et al*. 2000; Rickels *et al*. 2003), thus short-term adjunct benzodiazepine therapy is common when initiating treatment with these agents. For benzodiazepines, cognitive effects, rebound anxiety, withdrawal symptoms, and abuse potential, limit their use in clinical practice (Chouinard, 2004), while SSRIs and SNRIs are associated with sexual dysfunction (Bandelow *et al*. 2008) and discontinuation effects (Fava *et al*. 2007).

Extended-release quetiapine fumarate (quetiapine XR) offers a potential treatment option for GAD. While an augmentation study with a small sample size (6/11 patients completed) reported no additional benefit when quetiapine was added to paroxetine controlled release (Simon *et al*. 2008), other studies have reported positive efficacy results for quetiapine as either monotherapy or adjunct therapy in patients with GAD (Adson *et al*. 2004; Galynker *et al*. 2005; Katzman *et al*. 2008*b*). This study evaluated the efficacy and tolerability of quetiapine XR as once-daily monotherapy for GAD.

Method

Study design

This was a 10-wk multicentre, double-blind, parallel-group, placebo- and active- (paroxetine) controlled study. Paroxetine was included for assay sensitivity. After withdrawal of previous medication during a 1- to 4-wk enrolment/wash-out period, eligible patients entered an 8-wk, randomized, active treatment period, followed by a 2-wk drug-discontinuation phase.

The study was approved by institutional review boards for each study site and performed in accordance with the WMA Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. After complete description of the study to the patients, written informed consent was obtained.

Patients

Eligible patients were male or female (18–65 yr), with a documented diagnosis of GAD according to DSM-IV-TR criteria 300.02, as assessed by the Mini-International Neuropsychiatric Interview.

Patients were required to have a Hamilton Rating Scale for Anxiety (HAMA) total score $\geqslant 20$ with item 1 (anxious mood) and item 2 (tension) scores $\geqslant 2$ [administered using the Structured Interview Guide for the HAMA (SIGH-A)], a Montgomery–Åsberg Depression Rating Scale (MADRS) total score $\leqslant 16$, and a Clinical Global Impression – Severity of Illness (CGI-S) score $\geqslant 4$ at enrolment and randomization.

Exclusion criteria included: diagnosis of any DSM-IV-TR Axis I disorder other than GAD within 6 months prior to enrolment or any DSM-IV-TR Axis II disorder that could interfere with the patient's ability to participate in the study, a current serious suicidal or homicidal risk or a MADRS item 10 (suicidality) score $\geqslant 4$ or a suicide attempt during the 6 months prior to enrolment, substance or alcohol abuse within 6 months prior to enrolment or a clinically significant deviation from reference ranges in clinical laboratory test results.

Prior to randomization, patients could not have received: antipsychotic, hypnotic, or antidepressant medications (including benzodiazepines) within 7 d; monoamine oxidase inhibitors or mood stabilizers within 14 d; or fluoxetine within 28 d. Patients were permitted to receive psychotherapy during the study period if it had been ongoing for a minimum of 3 months prior to randomization.

Patients were assigned an enrolment code and a centre-specific randomization schedule was prepared from which allocation-numbered drug kits were packaged and shipped to centres. Patients were randomized to 50 mg or 150 mg quetiapine XR, 20 mg

paroxetine, or placebo, in a ratio of 1:1:1:1. The randomization list was generated using an internally developed and validated computer-based randomization system.

Packaging was identical for all study treatments; placebo tablets for quetiapine XR were identical to 50 mg quetiapine XR. Paroxetine placebo capsules were identical to 20 mg paroxetine over-encapsulated tablets. A double-dummy method was used to ensure that the number of tablets/capsules dispensed was the same across all treatment groups. Study treatments were administered orally, once-daily in the evening.

All patients randomized to 50 mg quetiapine XR or 20 mg paroxetine were initiated and maintained at this dose. Patients randomized to 150 mg quetiapine XR started at 50 mg on day 1, and increased to their target dose of 150 mg (3×50 mg tablets) on day 3. All treatments were discontinued at the end of the study, with no down-titration of dose.

Concomitant medication

Use of other psychoactive medication was not permitted, except medications for insomnia. The following medications were permitted twice weekly up to week 2, but not on the night before study assessments: 10 mg zolpidem tartrate, 1 g chloral hydrate, 20 mg zaleplon, 7.5 mg zopiclone. During the randomized treatment period, centrally acting anticholinergics were permitted for extrapyramidal symptoms (EPS), but were not given prophylactically.

Efficacy evaluations

The primary efficacy variable was mean change in HAMA total score from randomization at week 8. Additional evaluations included change in HAMA total score from randomization at day 4 and throughout, HAMA response ($\geqslant$50% decrease in total score from randomization) rate and change from randomization in HAMA psychic and somatic cluster scores at day 4 and week 8, and HAMA remission (total score $\leqslant$7) rate, CGI-S score, proportion of patients with a CGI-S score of 1 ('normal, not ill at all'), proportion of patients with a CGI-Improvement (CGI-I) score of 1 or 2 ('very much/much improved'), and change from randomization in MADRS total score at week 8. Quality of sleep was assessed at randomization and week 8 using the Pittsburgh Sleep Quality Index (PSQI; Buysse *et al*. 1989).

A *post-hoc* analysis was conducted to evaluate the difference in HAMA total scores between patients receiving quetiapine XR (pooled doses) with and without adverse events (AEs) relating to somnolence (including sedation, lethargy or sluggishness).

Clinical assessments of HAMA, CGI-S, and MADRS total scores were conducted at enrolment (visit 1, baseline), day 1 (visit 2, randomization), day 4 (visit 3), and at weeks 1, 2, 3, 4, 6, and 8 (visits 4–9). CGI-I scores were determined at visits 3–9. To ensure consistency throughout the study, each rater administering the HAMA, MADRS, and CGI scales received training in conducting these assessments. Certification was required for HAMA and MADRS scale assessment administration and raters were approved by the sponsor. For CGI scales, rater training was required to conduct these assessments. To reduce scoring variability, it was also recommended that the same rater conduct all assessments for a given patient for a specific scale. Only qualified physician raters administered the CGI. Rater training was performed by United BioSource Corporation (USA), who independently demonstrated high levels of inter-rater agreement ($\kappa = 0.889$) in this study (Kott *et al*. 2008).

Safety and tolerability assessments

The incidence, severity, and withdrawals because of AEs were recorded throughout. All AEs and serious AEs (SAEs), including any ongoing at study end or discontinuation, were followed up until resolution or until the investigator decided that no further follow-up was necessary. Tolerability was assessed through physical examination and 12-lead electrocardiogram (ECG) recordings (enrolment and week 8), laboratory measurements (enrolment, week 4, week 8), and recording of body weight, vital signs, and concomitant medication (enrolment and all subsequent visits). The self-administered, 14-item Changes in Sexual Functioning Questionnaire (CSFQ) was completed at randomization and weeks 2, 4, and 8, with separate versions for males and females (Keller *et al*. 2006). Barnes Akathisia Rating Scale (BARS) and Simpson–Angus Scale (SAS) scores were assessed at randomization and weeks 2, 4, 6, and 8. All investigators performing BARS and SAS ratings received instructions on how to use these scales and it was recommended that the same rater conduct all assessments for a given patient.

During the 2-wk drug-discontinuation phase, treatment discontinuation signs and symptoms (TDSS) were measured using a modified 18-item TDSS scale (Michelson *et al*. 2000), which included the additional AEs vomiting, nausea, and insomnia. Patients completing the randomized period were asked to rate discontinuation symptoms using the TDSS scale on post-treatment days 1, 3, 5, 7, and 14. During the

drug-discontinuation phase patients were encouraged not to take any medication for anxiety.

Statistical analysis

Intent-to-treat (ITT) populations include all randomized patients who received $\geqslant 1$ dose of study drug, and had $\geqslant 1$ post-treatment HAMA; for the analysis of primary and secondary efficacy variables in this study, a modified ITT (MITT) population was used, which had the additional criteria of a valid baseline HAMA total score assessment. The drug-discontinuation-phase (TDSS) population included patients who completed 8 wk of double-blind treatment and had baseline (week 8) and $\geqslant 1$ post-baseline TDSS assessments. The safety population included patients who received $\geqslant 1$ dose of study drug.

The target sample size was 186 patients per treatment group based on an anticipated treatment difference of 2.75 units from placebo and a standard deviation (S.D.) of 7.5 for the change in the primary outcome variable. This sample size provided a 90% power to show that either quetiapine XR dose was different from placebo. The study was not powered for a comparison of quetiapine XR *vs*. paroxetine.

The statistical significance of change in HAMA total scores from randomization at week 8 (primary efficacy variable) was determined using an analysis of covariance (ANCOVA) model that included terms for baseline score, treatment, and centre, and used the last observation carried forward (LOCF) approach for imputation of missing data. For the change in HAMA total scores at each time-point, statistical significance was determined for observed case (OC) data using the mixed model repeated-measures (MMRM) analysis, which included terms for treatment, baseline HAMA total score, visit, and treatment/visit interaction.

To ensure the overall significance level of 0.05 was preserved for the primary variable, a Bonferroni–Holm multiple testing procedure (MTP) for groups of hypotheses was applied to both quetiapine XR treatment groups. Pairwise differences between the least squares means (LSMs) for quetiapine XR treatment groups and placebo were calculated and nominal 95% confidence intervals (CIs) provided. Comparisons between paroxetine and placebo were not adjusted for multiplicity.

All other continuous variables were analysed using the same ANCOVA model as the primary efficacy variable, without adjustment for multiplicity. Binary data were analysed using logistic regression, with centre included as a random effect. Descriptive statistics were provided for all variables. Statistical analyses were two-sided and p values $<5\%$ denoted statistical significance.

Results

Patient population

Of 1054 recruited patients, 873 patients met the inclusion criteria and were randomized to receive 50 mg quetiapine XR ($n=221$), 150 mg quetiapine XR ($n=218$), paroxetine ($n=217$), or placebo ($n=217$) at centres in Europe [Bulgaria (76 patients, nine centres), Czech Republic (113 patients, 10 centres), Denmark (58 patients, four centres), Finland (85 patients, six centres), France (109 patients, 11 centres), Germany (35 patients, eight centres), Norway (16 patients, four centres), Romania (48 patients, five centres), Slovakia (27 patients, six centres), Spain (19 patients, four centres), Sweden (39 patients, six centres)], Argentina (59 patients, 11 centres), Canada (95 patients, 17 centres), Mexico (25 patients, four centres), and South Africa (69 patients, seven centres) between 18 May 2006 and 15 February 2007. The safety population comprised 870 patients (three patients did not receive treatment) and the MITT population included 866 patients (four additional patients were excluded due to missing/invalid baseline or post-randomization HAMA total scores).

The demographic and clinical characteristics of the treatment groups were generally well matched (Table 1). The proportion of patients completing the 10-wk study and reasons for early withdrawal are shown in Fig. 1.

Before study entry, 12.1%, 2.8%, and 15.1% of patients were receiving SSRIs, SNRIs, or benzodiazepines, respectively. The percentage of patients receiving concomitant sleep medication at any time (weeks 1–8) was: 50 mg quetiapine XR $\leqslant 1.5\%$, 150 mg quetiapine XR $\leqslant 3.2\%$, paroxetine $\leqslant 3.3\%$, and placebo $\leqslant 3.8\%$.

Efficacy

HAMA total scores were significantly reduced from randomization at week 8 for 50 mg quetiapine XR (-13.95, $p<0.05$), 150 mg quetiapine XR (-15.96, $p<0.001$), and paroxetine (-14.45, $p<0.01$) *vs*. placebo (-12.30) (Table 2, Fig. 2*a*). The level of significance (determined by MTP analysis) for 50 mg and 150 mg quetiapine XR *vs*. placebo was $p\leqslant 0.05$ and $p\leqslant 0.025$, respectively.

HAMA total scores were significantly reduced with 50 mg quetiapine XR (-4.43, $p<0.001$) and 150 mg

Table 1. Demographics and baseline characteristics (modified intent-to-treat population)

	Quetiapine XR 50 mg ($n=219$)	Quetiapine XR 150 mg ($n=216$)	Paroxetine 20 mg ($n=214$)	Placebo ($n=217$)
Gender, *n* (%)				
Male	70 (32.0)	72 (33.3)	76 (35.5)	82 (37.8)
Female	149 (68.0)	144 (66.7)	138 (64.5)	135 (62.2)
Age, yr				
Mean (S.D.)	40.7 (11.6)	42.3 (12.4)	41.6 (11.8)	41.2 (12.8)
Range	18 to 65	18 to 65	19 to 64	18 to 65
Ethnicity, *n* (%)				
White	202 (92.2)	206 (95.4)	205 (95.8)	204 (94.0)
Black	9 (4.1)	9 (4.2)	9 (4.2)	10 (4.6)
Asian	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Other	7 (3.2)	1 (0.5)	0 (0.0)	3 (1.4)
Weight, mean (S.D.) kg	72.1 (16.9)	73.2 (17.3)	74.6 (17.4)	74.6 (17.7)
BMI, mean (S.D.) kg/m²	25.4 (5.2)	25.9 (5.7)	26.1 (5.6)	25.9 (5.2)
Time since first onset of anxiety symptoms				
Mean (S.D.), yr	12.1 (11.6)	11.4 (11.2)	11.3 (11.1)	11.4 (11.6)
Min to max	1 to 52	1 to 56	1 to 52	1 to 55
Rating scale scores				
HAMA total				
Mean (S.D.)	26.9 (4.2)	26.6 (4.2)	27.1 (4.0)	27.3 (4.4)
Min to max	20 to 44	14 to 42	20 to 43	20 to 40
MADRS total				
Mean (S.D.)	11.5 (3.2)	11.3 (3.1)	11.3 (3.1)	11.5 (3.4)
Min to max	0 to 16	0 to 19	2 to 20	2 to 25
CGI-S				
Mean (S.D.)	4.8 (0.7)	4.8 (0.7)	4.8 (0.7)	4.8 (0.7)
Min to max	4 to 6	3 to 6	4 to 7	4 to 6

BMI, Body mass index; HAMA, Hamilton Rating Scale for Anxiety; MADRS, Montgomery–Åsberg Depression Rating Scale; CGI-S, Clinical Global Impression – Severity of Illness.

quetiapine XR (-3.86, $p<0.05$) *vs.* placebo (-2.90) at day 4, and each subsequent visit (Fig. 2*b*).

At day 4, HAMA response rates were significantly greater with 50 mg quetiapine XR *vs.* placebo; at week 8 they were significantly greater for all active treatment groups *vs.* placebo (Table 2). Remission rates at week 8 were significantly greater with 150 mg quetiapine XR and paroxetine *vs.* placebo (Table 2).

The results for other secondary efficacy variables are shown in Table 2. At week 8, both doses of quetiapine XR were associated with significant improvements in CGI-S, HAMA psychic cluster, PSQI global, and MADRS total scores *vs.* placebo, while significant improvements in HAMA somatic cluster scores and the proportion of patients with a CGI-I score $\geqslant 2$ occurred with 150 mg quetiapine XR.

Post-hoc *analysis of HAMA total score and somnolence*

The change in HAMA total score from randomization at week 8 was similar for patients receiving quetiapine XR with (-14.90, $n=133$) or without (-14.95, $n=302$) reporting AEs related to somnolence, and significantly greater than for placebo (-12.29, $n=217$, $p\leqslant 0.01$ and $p\leqslant 0.001$, respectively).

Safety and tolerability

10-wk study period (*8-wk randomized treatment and 2-wk drug-discontinuation phase*)

The overall incidence of AEs reported by patients (%) was higher in active treatment groups (quetiapine

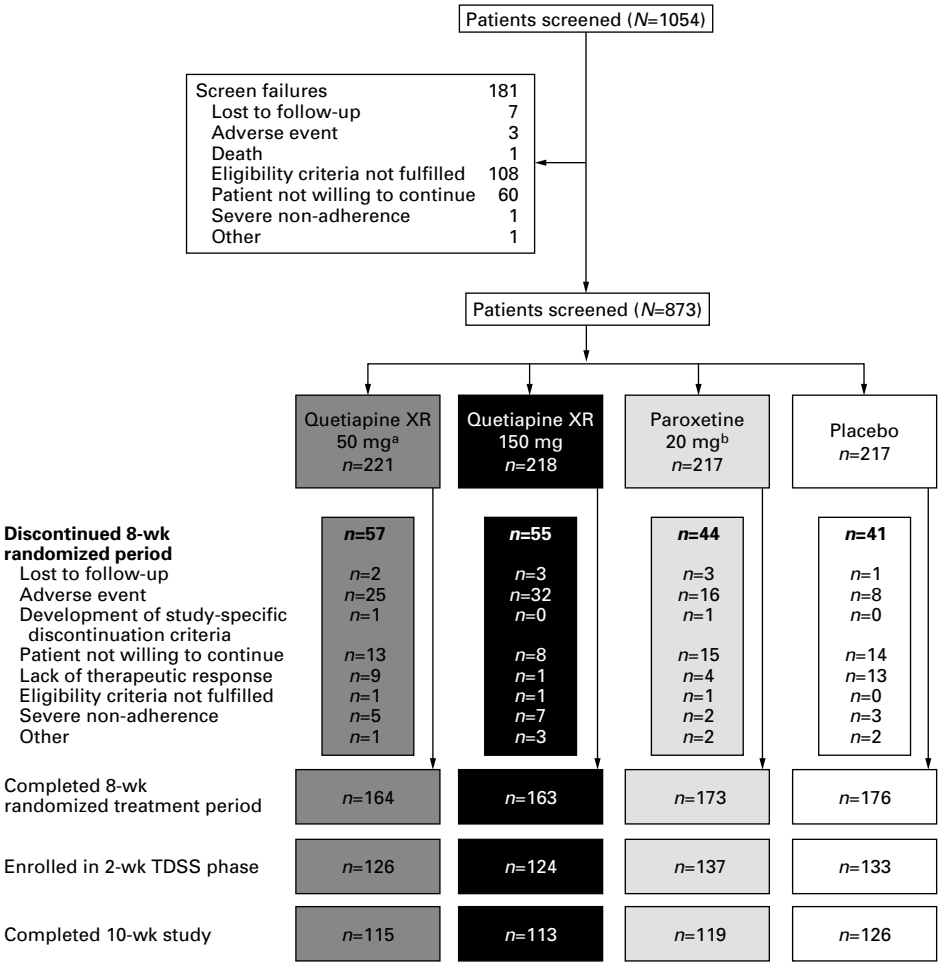

Fig. 1. Participant flow. [a] One patient was not treated. [b] Two patients were not treated. These patients were included in the discontinued-from-study drug analysis set but were not included in the safety analysis.

XR: 50 mg, 70.9%; 150 mg, 76.1%; paroxetine, 72.6%) compared to placebo (55.8%). The incidence of SAEs was low in all treatment groups (<1.4%) and none were considered treatment-related. The percentage of AEs considered treatment-related was higher in the quetiapine XR (50 mg, 58.6%; 150 mg, 65.6%) and paroxetine (58.6%) groups compared to placebo (34.6%). Discontinuations due to an AE were 11.8%, 16.1%, 7.9%, and 4.1% in the 50-mg and 150-mg quetiapine XR, paroxetine, and placebo groups, respectively.

8-wk randomized treatment period

Table 3 shows AEs (treatment-related or not) occurring in >5% of patients and AEs potentially related to sexual dysfunction or EPS.

The most frequent AEs leading to discontinuation were fatigue ($n=7$) and somnolence ($n=6$) (50 mg quetiapine XR), somnolence ($n=11$) and fatigue ($n=7$) (150 mg quetiapine XR), insomnia ($n=5$), and dizziness and fatigue (each $n=4$) (paroxetine); no AE leading to withdrawal occurred in >1 patient in the placebo group.

There was a slight improvement in sexual functioning in all treatment groups. The largest improvements (OC) in CSFQ occurred in the quetiapine XR groups [mean (S.D.) change: 50 mg, 2.3 (7.4), 150 mg, 2.1 (8.1), paroxetine, 0.7 (7.0), placebo, 1.1 (6.6)] and were similar by gender, with a numerical advantage for females with quetiapine XR over placebo and paroxetine.

At week 8, across treatment groups mean decreases in SAS and BARS were −0.1 to −0.2, and −0.1, respectively. During the randomized treatment period, centrally acting anticholinergics were used at any week by ⩽0.5% (placebo), ⩽0.6% [quetiapine XR (both doses)], and ⩽1.1% (paroxetine) of patients.

At week 8, there were no clinically relevant mean changes from baseline in vital signs, ECG, haematology, or clinical laboratory parameters; however, higher mean increases in supine pulse and ECG heart rate were observed with 150 mg quetiapine XR, compared to placebo. Mean changes in glucose and lipid parameters, and weight, and clinically relevant shifts in these parameters, are shown in Table 3.

2-wk drug-discontinuation phase

Of the patients completing the 8-wk randomized treatment period, 76.8% (50 mg quetiapine XR), 76.1% (150 mg quetiapine XR), 79.2% (paroxetine), and 75.6% (placebo) enrolled in the 2-wk drug-discontinuation phase (Fig. 1). Five patients discontinued due to AEs during the post-treatment period: quetiapine XR 150 mg, $n=3$ [moderate vertigo, moderate sedation, and mild depression (same patient), moderate nausea], paroxetine, $n=1$ (severe back pain), and placebo, $n=1$ (severe peritonitis). Table 2 shows mean TDSS total scores.

The most frequently reported AEs during the drug-discontinuation phase were insomnia and nausea for quetiapine XR (both doses), and dizziness and anxiety for paroxetine (Table 3).

Discussion

This is the first randomized, placebo-controlled study to evaluate the efficacy of quetiapine XR for the treatment of GAD in a large patient population. These results demonstrate that quetiapine XR (50 mg and 150 mg) is an effective once-daily monotherapy for the treatment of outpatients with GAD. Although the study was not powered for a statistical non-inferiority comparison with paroxetine, changes in efficacy variables observed with quetiapine XR were of at least the same magnitude as those for paroxetine. The effect of quetiapine XR on reducing symptoms of anxiety was greater than that for placebo and this difference was observed as early as day 4. Significant separation from placebo was only seen at week 2 with paroxetine.

At day 4, statistically significant differences from placebo were seen with quetiapine XR on a number of outcome variables (HAMA total, psychic, and somatic scores, HAMA response rate, and CGI-S), but not with paroxetine. Although currently recommended as first-line for the long-term treatment of GAD, SSRIs and SNRIs have a 2–4 wk delay in onset of action (Gelenberg *et al*. 2000; Rickels *et al*. 2003). To date, pregabalin and (high-potency) benzodiazepines are the only other agents to demonstrate anxiolytic efficacy by week 1 (Montgomery, 2006; Rickels *et al*. 2005). However, as benzodiazepines are associated with dependency, rebound, and withdrawal issues (Chouinard, 2004), the early onset of response and apparent infrequent occurrence of withdrawal symptoms observed with quetiapine XR in this study are of benefit to patients experiencing anxiety symptoms.

The improvement in HAMA total, psychic, and somatic scores demonstrate that quetiapine XR is effective across a wide range of anxiety symptoms. The beneficial effect of paroxetine in treating somatic symptoms associated with GAD has been investigated in several studies (Ball *et al*. 2005; Pollack *et al*. 2001; Rickels *et al*. 2003). In the present study, paroxetine did not significantly improve somatic symptoms compared to placebo; however, our study was not designed or powered to test this hypothesis.

In addition to psychic and somatic symptoms, sleep disturbances are commonly reported by patients with GAD (Papadimitriou & Linkowski, 2005). Quetiapine XR was associated with significant improvements in sleep (PSQI global scores) and numerical improvements across a range of PSQI items (including sleep quality, latency, duration, habitual sleep efficacy, sleep disturbances, and frequency of sleep medication) compared to placebo. In the present study, patients randomized to receive paroxetine did not report significant improvements in sleep quality compared to placebo. In other placebo-controlled studies of paroxetine in patients with GAD, somnolence (15%) and insomnia (11%) were the most frequently reported nervous system AEs (GlaxoSmithKline, 2008) and these AEs occurred at similar rates in the present study. As would be expected based on data from previous clinical trials, both doses of quetiapine XR (50 mg and 150 mg) were associated with a higher incidence of somnolence (21.8%, 25.2%, respectively) than insomnia (3.2%, 0.9%, respectively). Identifying and helping patients with GAD who experience sleep disturbance are important components of the overall care for this disorder (Benca, 2001).

In this study, 23.5% of all patients receiving quetiapine XR reported somnolence as an AE, with an early time to onset. While somnolence may have influenced early improvements in PSQI scores, *post-hoc* analysis of the primary endpoint in patients reporting somnolence-related AEs, suggests that improvement in anxiety symptoms is related to an anxiolytic effect rather than somnolence.

Approximately 62% of patients with GAD have comorbid depression during their lifetime (Judd *et al*. 1998). Although patients fulfilling the criteria for a current episode of major depression were excluded

Table 2. Results for change from randomization at day 4 or week 8 for efficacy variables (MITT population; LOCF), quality of life sleep measures (PSQI; MITT population; LOCF), MADRS total scores (safety population; LOCF), and treatment withdrawal (TDSS) scores at post-treatment days 1, 7, and 14 (TDSS population; OC)

	Quetiapine XR 50 mg ($n=219$)	Quetiapine XR 150 mg ($n=216$)	Paroxetine 20 mg ($n=214$)	Placebo ($n=217$)
HAMA total score				
Day 4				
LSM change	−4.43	−3.86	−2.69	−2.90
Estimated difference *vs.* placebo (95% CI)	−1.53 (−2.32 to −0.75) $p<0.001$	−0.96 (−1.75 to −0.18) $p<0.05$	0.21 (−0.57 to 0.99) $p=0.593$	
Week 8				
LSM change	−13.95	−15.96	−14.45	−12.30
Estimated difference *vs.* placebo (95% CI)	−1.65 (−3.12 to −0.18) $p<0.05$	−3.66 (−5.13 to −2.19) $p<0.001$	−2.15 (−3.63 to −0.68) $p<0.01$	
HAMA response rate[a]				
Day 4, *n* (%)	12 (6.4) $p<0.05$	7 (3.7) $p=0.068$	5 (2.6) $p=0.139$	1 (0.5)
Week 8, *n* (%)	137 (62.6) $p<0.05$	153 (70.8) $p<0.001$	141 (65.9) $p<0.01$	113 (52.1)
HAMA remission rate[b]				
Week 8, *n* (%)	71 (32.4) $p=0.282$	92 (42.6) $p<0.01$	83 (38.8) $p<0.05$	59 (27.2)
HAMA psychic cluster[c]				
Day 4				
LSM change	−2.53	−2.38	−1.56	−1.58
Estimated difference *vs.* placebo (95% CI)	−0.95 (−1.42 to −0.48) $p<0.001$	−0.80 (−1.26 to −0.33) $p<0.001$	0.02 (−0.45 to 0.48) $p=0.937$	
Week 8				
LSM change	−7.42	−8.64	−7.70	−6.27
Estimated difference *vs.* placebo (95% CI)	−1.15 (−1.97 to −0.33) $p<0.01$	−2.37 (−3.19 to −1.55) $p<0.001$	−1.43 (−2.25 to −0.61) $p<0.001$	
HAMA somatic cluster[d]				
Day 4				
LSM change	−1.86	−1.45	−1.09	−1.29
Estimated difference *vs.* placebo (95% CI)	−0.57 (−1.03 to −0.11) $p<0.05$	−0.16 (−0.63 to 0.30) $p=0.482$	0.20 (−0.26 to 0.66) $p=0.395$	
Week 8				
LSM change	−6.54	−7.37	−6.74	−6.00
Estimated difference *vs.* placebo (95% CI)	−0.54 (−1.27 to 0.20) $p=0.153$	−1.37 (−2.11 to −0.63) $p<0.001$	−0.74 (−1.48 to −0.00) $p=0.050$	
CGI-S				
Day 4				
LSM change	−0.38	−0.35	−0.24	−0.20
Estimated difference *vs.* placebo (95% CI)	−0.18 (−0.28 to −0.07) $p<0.01$	−0.15 (−0.26 to −0.04) $p<0.01$	0.04 (−0.15 to 0.07) $p=0.498$	

Table 2 (*cont.*)

	Quetiapine XR 50 mg ($n=219$)	Quetiapine XR 150 mg ($n=216$)	Paroxetine 20 mg ($n=214$)	Placebo ($n=217$)
Week 8				
LSM change	−1.85	−2.10	−1.95	−1.53
Estimated difference *vs.* placebo (95% CI)	−0.32 (−0.55 to −0.09) $p<0.01$	−0.57 (−0.80 to −0.34) $p<0.001$	−0.42 (−0.65 to −0.18) $p<0.001$	
Week 8: CGI-S score of 1, *n* (%)	43 (19.6)	49 (22.7)	39 (18.2)	27 (12.4)
CGI-I				
Week 8: CGI-I score of 1 or 2, *n* (%)	140 (63.9)	154 (71.3)	140 (65.4)	121 (55.8)
	$p=0.082$	$p<0.01$	$p<0.05$	
PSQI (Week 8)				
Global score, LSM change (95% CI)	−4.42 (−4.97 to −3.86) $p<0.001$	−4.55 (−5.10 to −4.00) $p<0.001$	−3.29 (−3.84 to −2.73) $p=0.099$	−2.73 (−3.28 to −2.18)
Sleep quality, mean change (S.D.)	−1.0 (0.9)	−1.1 (0.9)	−0.8 (1.0)	−0.5 (0.8)
Sleep latency, mean change (S.D.)	−1.0 (1.2)	−1.0 (1.2)	−0.8 (1.1)	−0.5 (1.0)
Sleep duration, mean change (S.D.)	−0.8 (1.0)	−0.8 (0.9)	−0.5 (1.1)	−0.5 (0.8)
Habitual sleep efficiency, mean change (S.D.)	−0.8 (1.3)	−0.7 (1.4)	−0.6 (1.4)	−0.6 (1.4)
Sleep disturbances, mean change (S.D.)	−0.6 (0.7)	−0.6 (0.7)	−0.5 (0.7)	−0.3 (0.7)
Frequency of sleep medication, mean change (S.D.)	−0.5 (1.1)	−0.2 (1.1)	−0.2 (1.0)	−0.2 (1.0)
Daytime dysfunction, mean change (S.D.)	−0.4 (0.8)	−0.4 (0.9)	−0.7 (0.9)	−0.5 (0.9)
MADRS total score[e]				
Week 8				
LSM change	−4.14	−5.64	−4.63	−2.74
Estimated difference *vs* placebo (95% CI)	−1.40 (−2.39 to −0.41) $p<0.01$	−2.90 (−3.89 to −1.90) $p<0.001$	−1.89 (−2.89 to −0.90) $p<0.001$	
TDSS total score[f]				
	($n=126$)	($n=124$)	($n=137$)	($n=133$)
Post-treatment day 1	2.3 (3.2)	2.1 (2.0)	1.4 (2.0)	1.5 (1.7)
Post-treatment day 7	2.7 (3.2)	3.2 (3.2)	4.3 (3.9)	2.3 (2.4)
Post-treatment day 14	2.7 (3.2)	2.7 (2.9)	3.7 (3.7)	2.5 (2.8)

MITT, Modified intent-to-treat; LOCF, last observation carried forward; PSQI, Pittsburgh Sleep Quality Index; MADRS, Montgomery–Åsberg Depression Rating Scale; TDSS, treatment discontinuation signs and symptoms; OC, observed case; HAMA, Hamilton Rating Scale for Anxiety; CI, confidence interval; LSM, least squares means; CGI-S, Clinical Global Impression – Severity of Illness; CGI-I, Clinical Global Impression – Improvement.

All *p* values *vs.* placebo.

[a] $\geqslant$50% reduction in HAMA total score from baseline.

[b] HAMA total score $\leqslant$7.

[c] Consisting of the following items: anxious mood, tension, fears, insomnia, intellectual changes, depressed mood, and behaviour symptoms.

[d] Consisting of the following items: muscular, sensory and cardiovascular, respiratory, gastrointestinal, genitourinary, and autonomic system disturbances.

[e] Safety population.

[f] Observed cases; drug-discontinuation phase population.

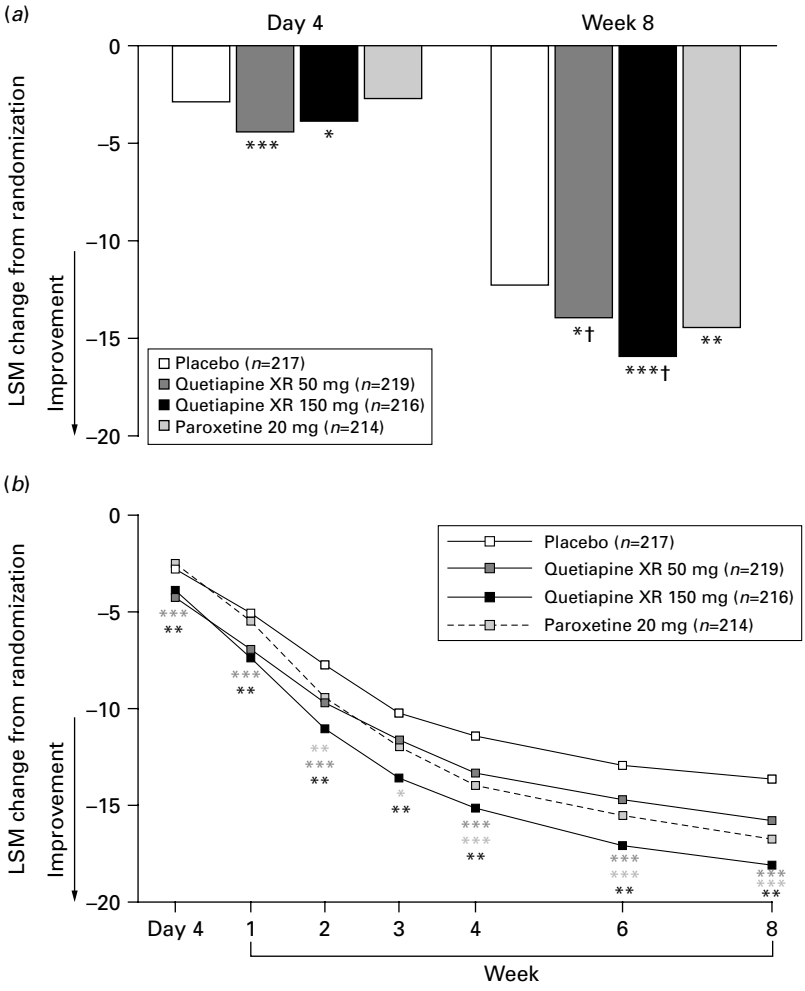

Fig. 2. Change in HAMA total score from randomization. (*a*) At day 4 and week 8 (MITT population; LOCF); * $p<0.05$, ** $p<0.01$, *** $p<0.001$ *vs.* placebo; † p value adjusted for multiplicity. (*b*) Over time (MITT population; OC, MMRM); * $p<0.05$, ** $p<0.01$, *** $p<0.001$ *vs.* placebo.

from this study, improvements in MADRS total scores indicate that quetiapine XR monotherapy reduces depressive symptoms in non-depressed patients with GAD compared to placebo; paroxetine also improved MADRS total scores.

AEs were reported by patients in all treatment groups. The pattern of common AEs, incidence of AEs of special interest, and changes in clinical laboratory results and vital signs for the quetiapine XR treatment groups were consistent with the known pharmacological and safety profile of quetiapine (Arvanitis *et al*. 1997; Timdahl *et al*. 2007). In this study, the proportion of patients reporting AEs related to sexual dysfunction was higher for paroxetine than for either quetiapine XR dose or placebo.

The incidence of spontaneously reported EPS-related AEs with quetiapine XR was low and these were generally mild to moderate in intensity. These results were confirmed by the assessment of parkinsonian and akathisia symptoms using SAS and BARS scores, which indicated a similar magnitude of change in the quetiapine XR (50 mg, 150 mg) and placebo treatment groups. While atypical antipsychotics are associated with a lower risk for EPS than conventional antipsychotics, it is important that patients are monitored for the emergence of events potentially related to EPS (Casey, 2006). EPS-like symptoms have also been reported with SSRI and SNRI treatments (Leo, 1996) and in the present study paroxetine was associated with a higher incidence of EPS-related AEs than either quetiapine XR or placebo.

Laboratory data revealed no clinically relevant changes in glucose, total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein

(LDL)-cholesterol, or triglycerides in patients receiving quetiapine XR; however, large variability in these data limits interpretation. Numerical increases in glucose levels and triglycerides were seen in this trial for quetiapine XR, compared to placebo. Elevations of these parameters are consistent with the known pharmacological profile of quetiapine in other disorders.

Patients in both quetiapine XR groups experienced an increase in mean weight, and a higher percentage of patients reported weight gain $\geqslant 7\%$ during the study, compared to placebo-treated patients. The mean change in body weight in this study (0.6–1.1 kg) is similar to that reported in two acute studies of quetiapine XR in patients with schizophrenia (Ganesan *et al*. 2008; Kahn *et al*. 2007). Longer-term studies are needed to evaluate these metabolic effects during maintenance treatment for GAD. Weight increases have also been observed with SSRIs and with other antidepressants (Fava, 2000). Paroxetine has been shown to cause weight gain (Marks *et al*. 2008). In the present study, mean increase in weight with paroxetine was similar to that seen with placebo, although the proportion of patients with weight gain $\geqslant 7\%$ was greater than in the placebo group.

The present study was designed to evaluate quetiapine XR in the acute treatment of GAD and therefore lasted for 10 wk, including 8 wk of active treatment. The changes in laboratory parameters and weight in this study are consistent with observations in short-term monotherapy studies from the quetiapine XR clinical programme in patients with major depressive disorder (Cutler *et al*. 2009; Weisler *et al*. 2009). Publication of results from a completed maintenance study investigating quetiapine XR in patients with GAD is awaited.

Paroxetine was administered at a dose of 20 mg in this study; however, higher doses (up to 60 mg) have been used in clinical trials of GAD. Nonetheless, in one fixed-dose study, 40 mg paroxetine did not show significantly greater improvement than 20 mg for the treatment of GAD (Rickels *et al*. 2003). The 20-mg dose utilized in our study is in accordance with the paroxetine prescribing information. Although it is usually recommended to dose paroxetine in the morning, this agent was administered in the evening throughout the study to maintain blinding.

Lower daily doses were possible in patients with GAD compared the recommended dose range for patients with schizophrenia (400–800 mg) and a once-daily, evening dosing regimen could be utilized with the XR formulation of quetiapine.

Due to the exclusion of patients with comorbid depression, which is standard procedure in clinical trials of anxiety disorders, the patient population in our study may not be truly representative of patients with GAD in clinical practice. Notably, quetiapine is effective in, and is approved for, the treatment of bipolar depression (Calabrese *et al*. 2005; Thase *et al*. 2006) and quetiapine XR has proven efficacy in treating depressive symptoms (Bauer *et al*. 2009; Cutler *et al*. 2009; Weisler *et al*. 2009). A specific measure of disability was not utilized in the present study as such scales are often not sensitive to acute changes. It was therefore not possible to formally assess the baseline level of impairment or changes in functioning that may have occurred following treatment. However, quetiapine XR monotherapy was significantly more effective in maintaining improvements in Sheehan Disability Scale scores compared to placebo in a time-to-event ($\leqslant 52$ wk) multicentre, randomized-withdrawal, double-blind, long-term study (Katzman *et al*. 2008*a*); full publication of these results is awaited.

Although the precise mechanism of action is unknown, the anxiolytic efficacy demonstrated by quetiapine may be due to its actions on the dopamine, serotonin, and norepinephrine neurotransmitter systems, or a combination of these effects. Both quetiapine and norquetiapine (active human metabolite) have moderate to high affinity for dopamine D_2 and serotonin 5-HT_{2A} receptors and norquetiapine is a potent inhibitor of the norepinephrine transporter (Goldstein *et al*. 2008; Jensen *et al*. 2008). As most drugs that are effective in the treatment of anxiety disorders enhance serotonergic and/or noradrenergic neurotransmission, it may be assumed that the anxiolytic effects of quetiapine are achieved via antagonism at serotonin 5-HT_{2A} receptors by norquetiapine and quetiapine, and/or inhibition of norepinephrine reuptake by norquetiapine. Additionally, preclinical studies have shown that antagonism at D_2 receptors plays a role in the anxiolytic effect of quetiapine in rodents (Maciag *et al*. 2007).

GAD is a serious illness and many patients do not recover following adequate treatment with currently available pharmacotherapies. Moreover, many ($>40\%$) patients with GAD experience residual anxiety symptoms 6–12 yr after diagnosis (Tyrer & Baldwin, 2006; Yonkers *et al*. 2000). In general, treatment guidelines do not recommend the use of conventional antipsychotics for patients with GAD due to the associated risk of EPS; however, atypical antipsychotics may have utility in this patient population (Bandelow *et al*. 2008; IPAP, 2008). Nonetheless, when deciding upon a particular pharmacotherapy, it is important that any benefits associated with treatment are carefully measured against potential risks, taking

Table 3. Most frequently reported adverse events (AEs) (with an incidence of >5% in any group) during the 8-wk randomized treatment period and during the drug-discontinuation phase, AEs of special interest (sexual dysfunction and extrapyramidal symptoms) occurring during the 8-wk randomized treatment period, and changes in clinical laboratory parameters and body weight from baseline end of treatment (safety population)

	Quetiapine XR 50 mg ($n=220$)	Quetiapine XR 150 mg ($n=218$)	Paroxetine 20 mg ($n=215$)	Placebo ($n=217$)
Randomized treatment period, MedDRA preferred term, *n* (%)				
Dry mouth	35 (15.9)	56 (25.7)	21 (9.8)	13 (6.0)
Somnolence[a]	48 (21.8)	55 (25.2)	24 (11.2)	10 (4.6)
Fatigue	33 (15.0)	36 (16.5)	20 (9.3)	8 (3.7)
Dizziness	26 (11.8)	34 (15.6)	29 (13.5)	13 (6.0)
Headache	36 (16.4)	27 (12.4)	37 (17.2)	39 (18.0)
Sedation	14 (6.4)	18 (8.3)	5 (2.3)	1 (0.5)
Nausea	17 (7.7)	14 (6.4)	44 (20.5)	16 (7.4)
Constipation	10 (4.5)	13 (6.0)	6 (2.8)	3 (1.4)
Diarrhoea	7 (3.2)	8 (3.7)	12 (5.6)	10 (4.6)
Nasopharyngitis	7 (3.2)	5 (2.3)	13 (6.0)	8 (3.7)
Insomnia	7 (3.2)	2 (0.9)	20 (9.3)	9 (4.1)
Drug-discontinuation phase, MedDRA preferred term, *n* (%)				
Insomnia	10 (4.5)	17 (7.8)	9 (4.2)	5 (2.3)
Nausea	8 (3.6)	12 (5.5)	9 (4.2)	4 (1.8)
Anxiety	3 (1.4)	3 (1.4)	11 (5.1)	1 (0.5)
Dizziness	7 (3.2)	3 (1.4)	22 (10.2)	3 (1.4)
AEs of special interest, *n* (%)				
Sexual dysfunction[b]	2 (0.9)	4 (1.8)	16 (7.4)	5 (2.3)
Extrapyramidal symptoms[c]	15 (6.8)	11 (5.0)	18 (8.4)	4 (1.8)
Laboratory parameters				
Glucose (mg/dl)[d]				
Mean (S.D.) baseline	93.6 (11.1)	94.3 (13.3)	93.3 (12.4)	94.6 (11.7)
Mean (S.D.) change	−0.9 (16.6)	0.9 (12.7)	1.0 (12.2)	0.7 (11.4)
Patients with fasting glucose ⩾126 mg/dL at end of treatment, *n* (%)	2 (1.2)	1 (0.6)	3 (1.9)	3 (1.8)
Total cholesterol (mg/dl)[d]				
Mean (S.D.) baseline	200.6 (43.6)	201.9 (46.4)	202.7 (44.2)	199.3 (48.1)
Mean (S.D.) change	−0.4 (27.1)	1.1 (31.7)	0.9 (26.9)	0.8 (27.1)
Patients with fasting total cholesterol ⩾240 mg/dl at end of treatment, *n* (%)	9 (7.6)	11 (8.5)	14 (11.4)	7 (5.3)
LDL-cholesterol (mg/dl)[d]				
Mean (S.D.) baseline	118.0 (37.0)	120.0 (40.9)	121.4 (38.7)	116.9 (39.2)
Mean (S.D.) change	0.3 (24.6)	−0.7 (26.1)	1.1 (22.4)	1.6 (24.1)
Patients with fasting LDL-cholesterol ⩾160 mg/dl at end of treatment, *n* (%)	7 (5.6)	9 (6.7)	14 (10.6)	8 (5.8)
HDL-cholesterol (mg/dl)[d]				
Mean (S.D.) baseline	58.2 (17.2)	58.0 (15.7)	57.8 (17.2)	57.7 (17.5)
Mean (S.D.) change	−0.3 (9.6)	−2.0 (9.4)	−0.1 (9.7)	0.7 (8.6)
Patients with fasting HDL-cholesterol ⩽40 mg/dl at end of treatment, *n* (%)	6 (4.7)	8 (5.9)	3 (2.2)	12 (8.6)
Triglycerides (mg/dl)[d]				
Mean (S.D.) baseline	123.8 (74.0)	120.6 (71.3)	118.1 (64.7)	127.4 (86.2)
Mean (S.D.) change	−3.0 (56.8)	19.7 (67.5)	−0.2 (54.1)	−8.3 (64.1)
Patients with fasting triglycerides ⩾200 mg/dl at end of treatment, *n* (%)	7 (5.5)	18 (13.6)	8 (5.8)	6 (4.3)

Table 3 (*cont.*)

	Quetiapine XR 50 mg ($n=220$)	Quetiapine XR 150 mg ($n=218$)	Paroxetine 20 mg ($n=215$)	Placebo ($n=217$)
Prolactin (ng/ml)[e]				
Mean (S.D.) baseline	10.0 (8.8)	10.1 (9.9)	9.5 (5.8)	10.7 (9.8)
Mean (S.D.) change	−0.4 (5.9)	0.0 (10.7)	2.3 (17.1)	−1.0 (10. 7)
Weight (kg), mean (S.D.) change	0.6 (2.3)	1.1 (2.2)	0.0 (2.2)	0.1 (2.8)
Patients with a ⩾7% increase in body weight at end of treatment, *n* (%)	10 (4.6)	15 (6.9)	10 (4.7)	5 (2.3)

MedDRA, Medical Dictionary for Regulatory Activities; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
[a] The median times to first onset of somnolence were 2.0, 4.5, and 4.0 d for the quetiapine XR, paroxetine, and placebo groups, respectively.
[b] MedDRA preferred terms: anorgasmia, ejaculation disorder, libido decreased, loss of libido, orgasm abnormal, sexual dysfunction, spontaneous penile erection; three of these AEs were severe in intensity [150 mg quetiapine XR, $n=1$ (loss of libido); paroxetine, $n=2$ (one each of loss of libido and sexual dysfunction)].
[c] MedDRA preferred terms: akathisia, restlessness, tremor, extrapyramidal disorder, bradykinesia, dyskinesia, hypertonia, muscle rigidity, psychomotor hyperactivity; two of these AEs were severe in intensity, tremor in the 150 mg quetiapine XR group ($n=1$) and dyskinesia in the paroxetine group ($n=1$).
[d] Fasting documented by patient report of at least 8 h since last meal before blood draw for both baseline and post-baseline sampling.
[e] Normal prolactin range (double antibody radioimmunoassay): 2–20 ng/ml (males); 2–29 ng/ml (females).

into account the complete tolerability profile for a given agent as well as individual patient factors. As the present study is short term, additional relapse prevention studies are necessary to establish if the benefits of quetiapine XR in GAD are maintained over the longer term and to assess the tolerability profile in this setting.

In summary, results reported here show that quetiapine XR once-daily monotherapy is an effective and generally well-tolerated treatment for patients with GAD, with symptom improvement seen as early as day 4, and a positive influence on sleep disturbances. Thus, quetiapine XR may offer an alternative treatment option for patients with anxiety symptoms.

Appendix: Investigators involved in the study

Argentina: Ricardo Corral (Buenos Aires), Carlos Finkelsztein (Buenos Aires), Christian Lupo (Rosario), Miguel Márquez (Buenos Aires), Pedro Gargoloff (Buenos Aires), Julio Herrera (Mendoza), Roxana Galeno (Mendoza), Gerardo Garcia Bonetto (Córdoba), Alberto Bertoldi (Buenos Aires), Carlos Morra (Córdoba), Daniel Mosca (Buenos Aires); **Bulgaria**: Lubomir Jivkov (Sofia), Temenuzhka Mateva (Ruse), Stefan Todorov (Varna), Rinaldo Shishkov (Varna), Damjan Getev (Kardjali), Ognian Tanchev (Sofia), Emilia Veleva (Sofia), Georgi Parchev (Veliko Tarnova), Nadia Ivanova (Vratza); **Canada**: Guy Chouinard (Quebec, QC), Richard Bergeron (Gatineau, QC), Sanjay Siddhartha (Miramichi, NB), Raymond Matte (Sherbrooke, QC), Angelo Fallu (Sherbrooke, QC), Serge Lessard (Orleans, ON), Sunny Johnson (Mississauga, ON), Paul Latimer (Kelownanm BC), Ranjith Chandrasena (Chatham, ON), Muhammad Sayeed (Corner Brook, NL), Brian Ticoll (Markham, ON), Arun Ravindran (Toronto, ON), Mysore Renuka-Prasad (Saskatoon, SK), Javed Ali (Sydney, NS), Arthur David Kantor (Toronto, ON), Eric Giguere (Montreal, QC), Jacques Bradwejn (Ottawa, ON), Kevin Kjernisted (Vancouver, BC), Rama Prayaga (Brantford, ON), Anil Joseph, (Sudbury, ON); **Czech Republic**: Zdenek Solle (Praha), Erik Herman (Praha), Eva Soukupova (Plzen), Michaela Klabusayova (Brno), Ilona Divacka (Praha), Jaroslav Lestina (Praha), Jiri Pisvejc (Litomerice), Jiri Bilik (Olomouc), Juraj Rektor (Prerov), Jiri Rozkos (Prostejov); **Denmark**: Jesper Søgaard (København), Stig Rasmussen (Hillerød), Bjarne Bahr (København), Bjarne Nielsen (Hellerup), Kirsten Behnke (Frederiksberg), Erik Kjærsgaard Nielsen (Haderslev), Eivind Knutsen (Århus); **Finland**: Antti Ahokas (Helsinki), Anna Savela (Helsinki), Raili Kansanen (Helsinki), Riitta Jokinen (Turku), Jukka Penttinen

(Salo), Juhani Aer (Järvenpää); **France**: Joël Gailledreau (Elancourt), Eric Neuman (Le Pecq), Frédéric Chapelle (Toulouse), Christian Gaussares (Arcahon), Joël Pon (Toulouse), Mocrane Abbar (Nimes), Pierre Le Goubey (Cherbourg), Paule Khalifa (Toulouse), Jean Audet (Angouleme), Bertrand Baranovsky (Rennes), Christophe Dufour (La Valette du Var); **Germany**: Borwin Bandelow (Göttingen), Bernd Gestewitz (Bad Saarow), Alexander Schulze (Berlin), Klaus-Christian Steinwachs (Nürnberg), Serena Scarel (Unterhaching), Eugen Schlegel (Siegen), Andrej Pauls (München), Ansgar Frieling (Hamburg), Wolfgang Mattern (Bochum), Jana Thomsen (Berlin); **Mexico**: Sergio Javier Villaseñor Bayardo (Guadalajara), Susana García Cruz (Ciudad de México), Humberto Nicolini (Extremadura), Ricardo Secin (Colonia Héroes de Padierna), Felipe Ortega Zarzosa (San Luis Potosí), Juan Bautista Corral García (Ciudad de México); **Norway**: Espen Anker (Oslo), Dag Oulie (Fyllingsdalen), Ole Johan Høyberg (Brattvåg), Helge Istad (Oslo), Erik Øfjord (Paradis); **Romania**: Gabriela Marian (Bucharest), Cristian Marinescu (Arges), Marie Georgescu (Bucharest), Catalina Tudose (Bucharest), Irina Dan (Bucharest), Daniela Vulcu (Sibiu); **Slovakia**: Marek Zelman (Brezno), Eva Pálová (Kosice), Vladimír Garaj (Bojnice), Dagmar Strocholcova (Zilina-Bytcica), Zuzana Janíková (Liptovsky Mikulas), Livia Vavrusova (Bratislava); **South Africa**: Lynette Nel (Pretoria), V Agambaram (Durban), Irma Verster (Bloemfontein), Donald Wilson (Cape Town), Paul Carey (Cape Town), Paresh Ramjee (Pretoria), Dana Niehaus (Cape Town); **Spain**: José Ramón Doménech Bisén (Barcelona), Salvador Ros Montalbán (Barcelona), Antonio Higueras Aranda (Granada), Julio Bobes García (Asturias), Tomás Palomo Álvarez (Madrid), Angel Luís Montejo González (Salamanca); **Sweden**: Christer Engström (Sundsvall), Per Ekdahl (Malmö), Göran Johnson (Malmö), Kurt Wahlstedt (Uppsala), Ingemar Sjödin (Linköping), Peter Bosson (Lund).

Acknowledgements

This study (Silver: D1448C00011) was supported by AstraZeneca Pharmaceuticals. We thank Dr Kim Croskery, from Complete Medical Communications Limited, who provided medical writing support, funded by AstraZeneca. The author(s) are entirely responsible for the scientific content of the paper. Clinical Trials Registry number: NCT00322595. The study was registered at clinicaltrials.gov. NCT00322595 (http://clinicaltrials.gov/ct2/show/NCT00322595).

Statement of Interest

Borwin Bandelow has received consulting fees and honoraria within the last 3 years from AstraZeneca, Bristol–Myers Squibb, Cephalon, Dainippon-Sumitomo, Glaxo, Janssen, Jazz, Lilly, Lundbeck, Pfizer, Roche, Servier, Solvay, Wyeth and Xian-Janssen. Guy Chouinard has received consulting fees and honoraria within the last 3 years from Janssen-Cilag, Schering Plough, and BioLineRx. Julio Bobes has received consulting fees and honoraria within the last 3 years from AstraZeneca, GlaxoSmithKline, Janssen-Cilag, Lilly, and Pfizer. Antti Ahokas has received consulting fees and honoraria from Boehringer-Ingelheim, GlaxoSmithKline, Lilly, Lundbeck, Sanofi-Aventis, Servier, and Wyeth. Ivan Eggens, Hans Eriksson, and Sherry Liu are employees of AstraZeneca.

References

Adson DE, Kushner MG, Eiben KM, Schulz SC (2004). Preliminary experience with adjunctive quetiapine in patients receiving selective serotonin reuptake inhibitors. *Depression and Anxiety* **19**, 121–126.

Allgulander C, Dahl AA, Austin C, Morris PL, *et al.* (2004). Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. *American Journal of Psychiatry* **161**, 1642–1649.

Arvanitis LA, Miller BG, the Seroquel Trial 13 Study Group (1997). Multiple fixed doses of 'Seroquel' (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biological Psychiatry* **42**, 233–246.

Ball SG, Kuhn A, Wall D, Shekhar A, *et al.* (2005). Selective serotonin reuptake inhibitor treatment for generalized anxiety disorder: a double-blind, prospective comparison between paroxetine and sertraline. *Journal of Clinical Psychiatry* **66**, 94–99.

Bandelow B, Zohar J, Hollander E, Kasper S, *et al.* (2008). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive–compulsive and post-traumatic stress disorders – First Revision. *World Journal of Biological Psychiatry* **9**, 248–312.

Bauer M, Pretorius HW, Constant EL, Earley WR, *et al.* (2009). Extended release quetiapine fumarate as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. *Journal of Clinical Psychiatry* **70**, 540–549.

Benca RM (2001). Consequences of insomnia and its therapies. *Journal of Clinical Psychiatry* **62** (Suppl. 10), 33–38.

Buysse DJ, Reynolds III CF, Monk TH, Berman SR, *et al.* (1989). The Pittsburgh Sleep Quality Index: a new

instrument for psychiatric practice and research. *Psychiatry Research* **28**, 193–213.

Calabrese JR, Keck Jr. PE, Macfadden W, Minkwitz M, *et al.* (2005). A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *American Journal of Psychiatry* **162**, 1351–1360.

Casey DE (2006). Implications of the CATIE trial on treatment: extrapyramidal symptoms. *CNS Spectrums* **11**, 25–31.

Chouinard G (2004). Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. *Journal of Clinical Psychiatry* **65** (Suppl. 5), 7–12.

Cutler AJ, Montgomery SA, Feifel D, Lazarus A, *et al.* (2009). Extended release quetiapine fumarate monotherapy in major depressive disorder: a placebo- and duloxetine-controlled study. *Journal of Clinical Psychiatry* **70**, 526–539.

Fava GA, Bernardi M, Tomba E, Rafanelli C (2007). Effects of gradual discontinuation of selective serotonin reuptake inhibitors in panic disorder with agoraphobia. *International Journal of Neuropsychopharmacology* **10**, 835–838.

Fava M (2000). Weight gain and antidepressants. *Journal of Clinical Psychiatry* **61** (Suppl. 11), 37–41.

Galynker I, Khan A, Grebchenko Y, Ten A, *et al.* (2005). Low-dose risperidone and quetiapine as monotherapy for comorbid anxiety and depression. *Journal of Clinical Psychiatry* **66**, 544.

Ganesan S, Agambaram V, Randeree F, Eggens I, *et al.* (2008). Switching from other antipsychotics to once-daily extended release quetiapine fumarate in patients with schizophrenia. *Current Medical Research and Opinion* **24**, 21–32.

Gelenberg AJ, Lydiard RB, Rudolph RL, Aguiar L, *et al.* (2000). Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: a 6-month randomized controlled trial. *Journal of the American Medical Association* **283**, 3082–3088.

GlaxoSmithKline (2008). Paroxetine prescribing information. (http://us.gsk.com/products/assets/us_paxil.pdf).

Goldstein JM, Nyberg S, Brecher M (2008). Preclinical mechanisms for the broad spectrum of antipsychotic, antidepressant and mood stabilizing properties of Seroquel. *European Psychiatry* **23** (Suppl. 2), S202.

IPAP (2008). International Psychopharmacology Algorithm Project. Generalized anxiety disorder (GAD) algorithm (http://www.ipap.org/gad/).

Jensen NH, Rodriguiz RM, Caron MG, Wetsel WC, *et al.* (2008). N-Desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5-$HT_{(1A)}$ agonist, as a putative mediator of quetiapine's antidepressant activity. *Neuropsychopharmacology* **33**, 2303–2312.

Judd LL, Kessler RC, Paulus MP, Zeller PV, *et al.* (1998). Comorbidity as a fundamental feature of generalized anxiety disorders: results from the National Comorbidity Study (NCS). *Acta Psychiatrica Scandinavica* (Suppl. 393), 6–11.

Kahn RS, Schulz SC, Palazov VD, Reyes EB, *et al.* (2007). Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: a randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychiatry* **68**, 832–842.

Katzman MA, Brawman-Mintzer O, Reyes E, Olausson B, *et al.* (2008*a*). Quetiapine XR: maintenance therapy of generalised anxiety disorder. Poster presented at the XIV World Congress of Psychiatry, Prague, Czech Republic, 20–25 September.

Katzman MA, Vermani M, Jacobs L, Marcus M, *et al.* (2008*b*). Quetiapine as an adjunctive pharmacotherapy for the treatment of non-remitting generalized anxiety disorder: a flexible-dose, open-label pilot trial. *Journal of Anxiety Disorders* **22**, 1480–1486.

Keller A, McGarvey EL, Clayton AH (2006). Reliability and construct validity of the Changes in Sexual Functioning Questionnaire short-form (CSFQ-14). *Journal of Sex and Marital Therapy* **32**, 43–52.

Kott A, Cicchetti D, Markovic O, Spear C (2008). Assessing the ability of rater training to achieve good-to-excellent inter-rater reliability on the HAM-A using kappa statistics. *European Psychiatry* **23**, S214.

Leo RJ (1996). Movement disorders associated with the serotonin selective reuptake inhibitors. *Journal of Clinical Psychiatry* **57**, 449–454.

Maciag C, Smolka J, McLaughlin J, Hudzik T, *et al.* (2007). Anxiolytic effects of quetiapine in rat punished responding: mechanism of action and the role of D_2 antagonism. *European Neuropsychopharmacology* **17** (Suppl. 4), S399.

Marks DM, Park MH, Ham BJ, Han C, *et al.* (2008). Paroxetine: safety and tolerability issues. *Expert Opinion on Drug Safety* **7**, 783–794.

Mendels J, Krajewski TF, Huffer V, Taylor RJ, *et al.* (1986). Effective short-term treatment of generalized anxiety disorder with trifluoperazine. *Journal of Clinical Psychiatry* **47**, 170–174.

Michelson D, Fava M, Amsterdam J, Apter J, *et al.* (2000). Interruption of selective serotonin reuptake inhibitor treatment. Double-blind, placebo-controlled trial. *British Journal of Psychiatry* **176**, 363–368.

Montgomery SA (2006). Pregabalin for the treatment of generalised anxiety disorder. *Expert Opinion on Pharmacotherapy* **7**, 2139–2154.

Ninan PT (2001). Dissolving the burden of generalized anxiety disorder. *Journal of Clinical Psychiatry* **62** (Suppl. 19), 5–10.

Nutt D, Argyropoulos S, Hood S, Potokar J (2006). Generalized anxiety disorder: a comorbid disease. *European Neuropsychopharmacology* **16** (Suppl. 2), S109–S118.

Papadimitriou GN, Linkowski P (2005). Sleep disturbance in anxiety disorders. *International Review of Psychiatry* **17**, 229–236.

Pollack MH (2001). Optimizing pharmacotherapy of generalized anxiety disorder to achieve remission. *Journal of Clinical Psychiatry* **62** (Suppl. 19), 20–25.

Pollack MH, Zaninelli R, Goddard A, McCafferty JP, *et al.* (2001). Paroxetine in the treatment of generalized anxiety disorder: results of a placebo-controlled, flexible-dosage trial. *Journal of Clinical Psychiatry* **62**, 350–357.

Rickels K, Pollack MH, Feltner DE, Lydiard RB, *et al.* (2005). Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. *Archives of General Psychiatry* **62**, 1022–1030.

Rickels K, Weise CC, Feldman H, Fee EA, *et al.* (1978). Loxapine in neurotic anxiety: some modifiers of treatment response. *Journal of International Medical Research* **6**, 180–185.

Rickels K, Zaninelli R, McCafferty J, Bellew K, *et al.* (2003). Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. *American Journal of Psychiatry* **160**, 749–756.

Rubio G, Lopez-Ibor JJ (2007). Generalized anxiety disorder: a 40-year follow-up study. *Acta Psychiatrica Scandinavica* **115**, 372–379.

Simon NM, Connor KM, Lebeau RT, Hoge EA, *et al.* (2008). Quetiapine augmentation of paroxetine CR for the treatment of refractory generalized anxiety disorder: preliminary findings. *Psychopharmacology* (*Berlin*) **197**, 675–681.

Thase ME, Macfadden W, Weisler RH, Chang W, *et al.* (2006). Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *Journal of Clinical Psychopharmacology* **26**, 600–609.

Timdahl K, Carlsson A, Stening G (2007). An analysis of safety and tolerability data from controlled, comparative studies of quetiapine in patients with schizophrenia, focusing on extrapyramidal symptoms. *Human Psychopharmacology* **22**, 315–325.

Tyrer P, Baldwin D (2006). Generalised anxiety disorder. *Lancet* **368**, 2156–2166.

Weisler R, Joyce MJ, McGill L, Lazarus A, *et al.* (2009). Extended release quetiapine fumarate monotherapy for major depressive disorder: results of a double-blind, randomized, placebo controlled study. *CNS Spectrums* **14**, 299–313.

Yamamoto J, Kline FM, Burgoyne RW (1973). The treatment of severe anxiety in outpatients: a controlled study comparing chlordiazepoxide and chlorpromazine. *Psychosomatics* **14**, 46–51.

Yonkers KA, Dyck IR, Warshaw M, Keller MB (2000). Factors predicting the clinical course of generalised anxiety disorder. *British Journal of Psychiatry* **176**, 544–549.